REMARKS

The applicant appreciates the Examiner's acknowledgement and entry of the priority claim to provisional application 60/224,447, and notes a typographical error indicates that application was filed on August 10, 2002 while it should indicate that the application was filed on August 10, 2000.

Claims 14, 16, 39, 41-48 are pending and stand rejected. Claims 44 and 47 have been canceled, and claim 39 has been amended. The amendments are supported by the specification, e.g. by page 7, lines 1-15, and by the claims as originally filed, see for example original claim 9. The amendments thus add no new matter. Entry of the amendments and reconsideration in light of the following comments are respectfully requested.

35 U.S.C. § 101 Rejection

The Examiner has maintained a rejection of claim 48 as allegedly inoperative. The arguments presented in support of that rejection focus on the teachings of the Divieti reference and states that the Applicant's response was 'argument only,' focused on "what the prior art does not teach", and ignored the teachings of the reference. The Applicant traverses this rejection to the extent that it may remain relevant in light of the amendment.

Claim 48 says: "The method of claim 39, wherein the PTH antagonist has a further effect of blocking a PTH binding site on a PTH receptor, without concomitant activation of the PTH receptor in the subject."

To establish a rejection based on lack of utility, the Office must show that the claimed method does not provide a specific, substantial and credible utility. The Office has not analyzed utility in those terms: the Office asserts that the claimed invention is inoperative, based on a single reference describing a specific CPTH fragment, rather than providing evidence or reasoning to show that the legal standard for utility is not met. The cited reference describes only certain aspects of the activity of specific CPTH fragments. It does not discuss PTH antagonists commensurate with the

scope of the present claims, and it certainly does not recognize that such compounds have the activity demonstrated by the data in the application, as further discussed below; therefore it cannot demonstrate that the claimed methods are inoperative. Furthermore, patentability is not precluded by the presence of a single inoperative example within the scope of the claim: an inoperative embodiment, or several, within the claim scope does not even provide a basis for an enablement rejection, let alone a rejection based on utility. *Atlas Powder Co. v. E.I. duPont de Nemous & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984). Therefore the cited reference without more would not establish a 35 U.S.C. § 101 rejection even if it proved conclusively that an embodiment within the scope of the claims were inoperable—which the applicants do not understand it to do at all.

This claim is drawn to the effect of a PTH antagonist of claim 39 at "a PTH binding site on a PTH receptor"; it is not limited to a specific receptor or to a specific antagonist. Yet the Divieti reference relied on for the utility rejection relates only to specific receptors, and only in combination with certain CPTH fragments. It is credible that the PTH antagonists bind to other PTH receptors; it is entirely credible that they thereby preclude binding of PTH to provide a desirable biological effect; and it is quite credible that they thereby antagonize PTH binding, for example, without activating the receptor. Thus even if the reference showed that the claim would not operate for one specific embodiment, which the applicant maintains it does not, the applicant's focus on what is missing from the reference is believed to be proper and to be sufficient to overcome the stated rejection: the very limited scope of the reference without more simply does not and cannot establish that the claimed method is inoperative. Indeed, the claimed method, which incorporates the method steps of claim 39, is not inoperative unless the added claim limitations preclude the operability of the steps of claim 39. Withdrawal of this rejection is therefore requested.

35 U.S.C. § 112

Claims 39 and 41-48 stand rejected based on the relative term "excessive". The Office asserts that this term renders the claim scope indefinite. In view of the present amendment removing that term from claim 39, this rejection is moot.

Rejections of method claims based on 35 U.S.C. 102(b) and 103

Claims 39, 41, 42, 44 and 47 stand rejected over Fukuda, EP 0 528 271, alone or in combination with Takasu.

In the prior response, the Applicant's representative made an error in interpreting Fukuda. At page 23, Fukuda lists data, indicating that the data are for the muteins in Examples 2 to 6 (line 22). Two of these are named identically in the table as "[Leu^8] human PTH"—but the two adjacent listings have different activities, so they clearly represent two different species. These were interpreted by the applicant to refer to consecutive Examples 4 and 5, which describe two [Leu^8] PTH species, one corresponding to a mutein of PTH_{1-84} and the other to a mutein of PTH_{7-84}; however, as the Examiner appears to recognize (though without commenting on the obvious error in the reference), one of them is probably the Leu^{18} mutein of PTH_{1-84} rather than the [Leu^8] PTH_{7-84} mutein. This seems to be confirmed by a corresponding U.S. patent, where the table shows one of these as [Leu^{18}]. See US 5,856,138 at col. 30. While the misreading of Fukuda appeared to be a reasonable interpretation of its obvious error, it was apparently wrong. Thus the Fukuda reference actually does not show activity data for any N-truncated PTH species, even a mutein. The applicant's representative regrets any confusion created by the error.

Second, in view of the present amendment, these rejections are believed to be overcome. The present claims are drawn to the treatment of a subject having hypoparathyroidism. This represents a specific situation within the scope of previously presented claim 30, for example, where the PTH antagonists are used to treat hypercalcemia. The amendment is supported by the specification at page 7 and the graph in Figure 2 as well as e.g. original claim 9.

The graph in Figure 2 relates to serum calcium levels in rats that have had their parathyroid glands removed, and thus produce no PTH. Nevertheless, as shown in Figure 2 and described at page 7, lines 6-9, an injection of PTH_{7-84} lowered their serum calcium levels below that of controls—despite the absence of PTH. The rats have hypoparathyroidism (as stated at line 14) due to the removal of their parathyroid glands, and they still respond to PTH $_{7-84}$ as demonstrated by

the data; therefore their response is not due simply to antagonism of PTH as that term is ordinarily understood.

An antagonist is understood in the art to refer to a substance "opposing or resisting the action of another". See the definition of antagonist in Stedman's Medical Dictionary, 26th ed. (1995) **[Exhibit A]**. PTH antagonists of the claimed invention are shown by the data provided to do more than this. Clearly, in the cited references the PTH peptides are understood and used as traditional antagonists, substances used to oppose the effects of PTH. Thus the references at most suggest that such peptides can be used to reduce the effects of excessive PTH, so one of ordinary skill would have no reason to administer them to a subject deficient in PTH.

As the graph in Figure 2 shows, the claimed method reduces calcium levels in a subject having no PTH to counteract. One of ordinary skill unaware of the effects that the claimed peptides have on rats without PTH would have no reason to administer them to a subject deficient in PTH activity. Based on the cited references, one could not have a reasonable expectation of success at lowering the serum calcium level in such a subject using such substances, because the antagonism of PTH by such materials was the only mechanism by which they were known to act. In particular, Fukuda does not teach administering PTH antagonists to a subject having hypoparathyroidism: on the contrary, it teaches administering PTH agonists to such subjects. And it does not show or suggest that administering an antagonist to a subject with hypoparathyroidism would lower calcium levels: such subjects more typically have abnormally low calcium levels—but some forms of hypoparathyroidism result from or accompany high calcium levels. See, e.g., Abstract of Shimoda, et al., *Nippon Jinzo Gakkai Shi.*, 40:1, 1-7 (1998), which also shows that hypoparathyroidism can occur in renal osteodystrophy patients **[Exhibit B]**. And the antagonists of the present claims have an effect of lowering serum calcium levels in a hypoparathroidal subject, in the absence of PTH.

Fukuda describes some PTH peptides as PTH antagonists, but they are clearly understood to be antagonists in the conventional sense. As the examiner previously stated, the meaning of antagonists is well established: they are compounds that prevent another substance, in this case PTH, from causing certain effects. The references in Fukuda to using PTH antagonists to

treat hypercalcemia, and their use "as therapeutic agents for hypercalcemia and hyperparathyroidism" are very clearly understood in the context of that reference to refer only to treatment of the effects of elevated PTH activity. Those statements in Fukuda would not lead one skilled in the art to use a PTH antagonist to treat a subject having hypoparathyroidism, even to alleviate elevated calcium levels, because the PTH antagonist would not be expected to have that effect when PTH levels are too low. Thus the claimed methods are both novel and nonobvious over Fukuda; and the novelty and obviousness rejections based on Fukuda can be withdrawn.

Rejection of composition claims based on 35 U.S.C. § 101

Claims 14 and 16 were rejected as obvious over Fukuda in light of Takasu. The examiner asserts that Takasu teaches an hPTH antagonist with a minimum size of the fragment hPTH(35-84). This is incorrect: Takasu does not describe any PTH peptides larger than hPTH(35-84), except for hPTH(1-84) itself. Fukuda teaches only deletion of 3-6 residues from the N-terminus. Thus neither reference teaches any peptide of intermediate length between PTH(7-84) and PTH(35-84). The references therefore do not describe any peptides within the present claims. As the disclosure of all elements of the claimed invention is required for an obviousness rejection, the combined references do not provide a prima facie case for this rejection.

The Examiner then states that it would be instantly obvious that deletions between 3 and 34 residues would be expected to be PTH antagonists. However, as already established above, Fukuda provides NO data for inhibition by N-terminally truncated peptides, and the data in Takasu demonstrates significant variability of efficacy for its peptides, depending on their length: see, e.g., Figure 5.

Moreover, neither reference suggests making the present compositions of intermediate length, and the Examiner provides no reason for the ordinary practitioner to make them other than an assertion that "it would be instantly obvious." There is nothing cited from the references to suggest that peptides of intermediate length are desirable or that they would have superior activity or properties. While the motivation to combine references can come from the common knowledge

in the art, the courts consistently caution that the office must provide reasoning more substantial than an unsupported assertion that 'it would be obvious' as the basis for a 103 rejection: that requirement is an important protection against impermissible hindsight reconstruction of the claimed invention.

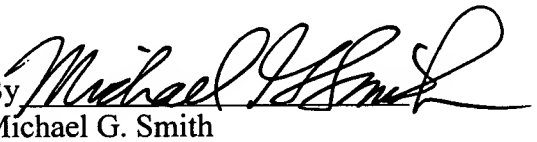
And even if it were considered obvious to try peptides of intermediate lengths as PTH antagonists, based on the reference one would have a hope of success rather than the requisite 'reasonable expectation' of success. Thus the Examiner has not established that the references provide all elements of the claimed invention, or motivation to combine the teachings of the reference, or a reasonable expectation of success. Therefore, a prima facie case for an obviousness rejection has not been established. Withdrawal of this rejection is thus requested.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 532212000300. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: October 21, 2005

Respectfully submitted,

By 

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